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Functional human variation

13.03.2013

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We are all different!

The human genome is ~3 x 10^9 base pairs of DNA
=> no two humans ever have been or will be genetically identical

Between any two humans, the amount of genetic variation is ~ 0.1%

~ one base pair out of every 1,000 will be different between any two individuals

Any two (diploid) people have about 6 x 10^6 base pairs that are different!

Genetic variation

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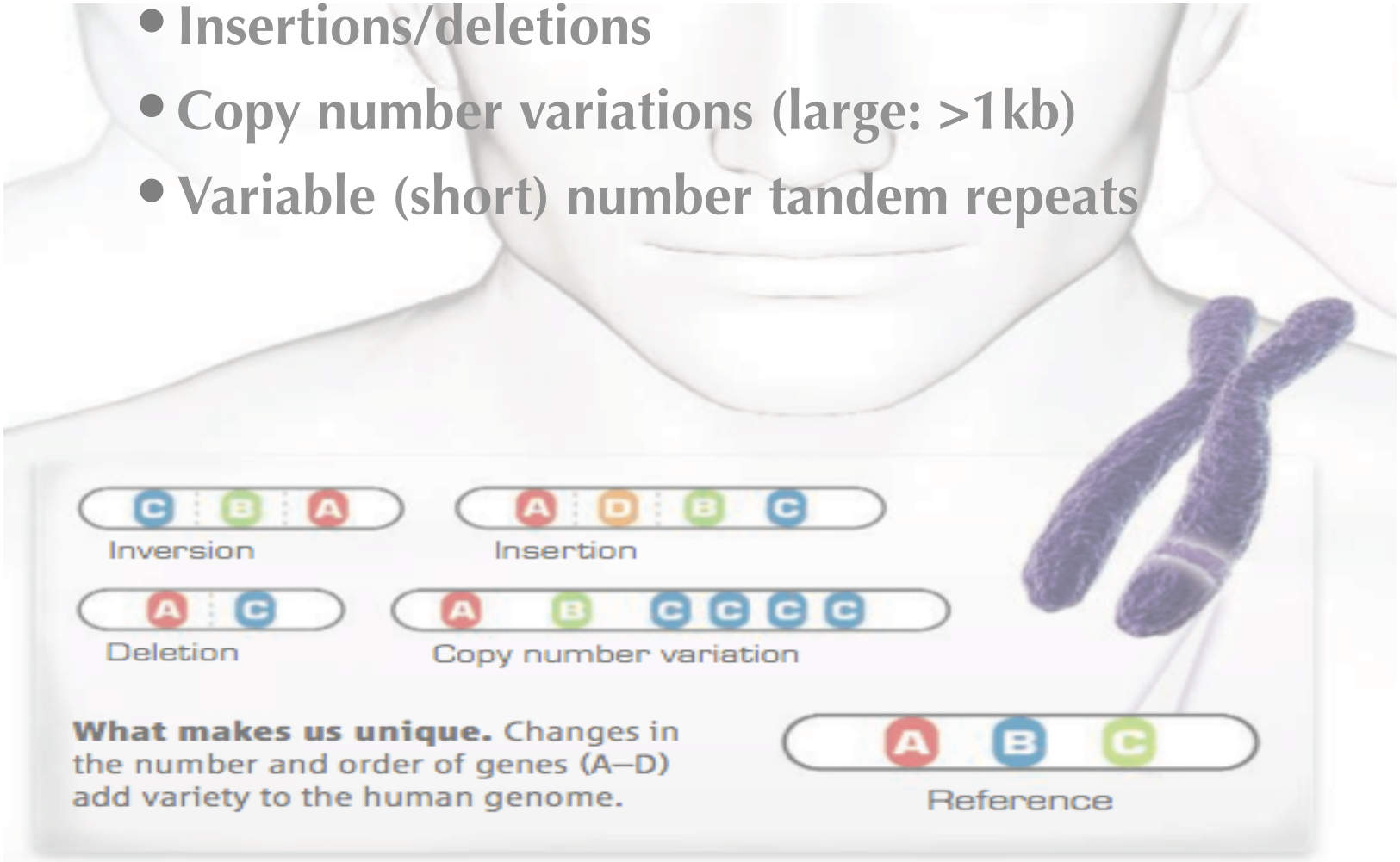
- **Single nucleotide polymorphisms (SNP)**
- Insertions/deletions
- Copy number variations (large: >1kb)
- Variable (short) number tandem repeats



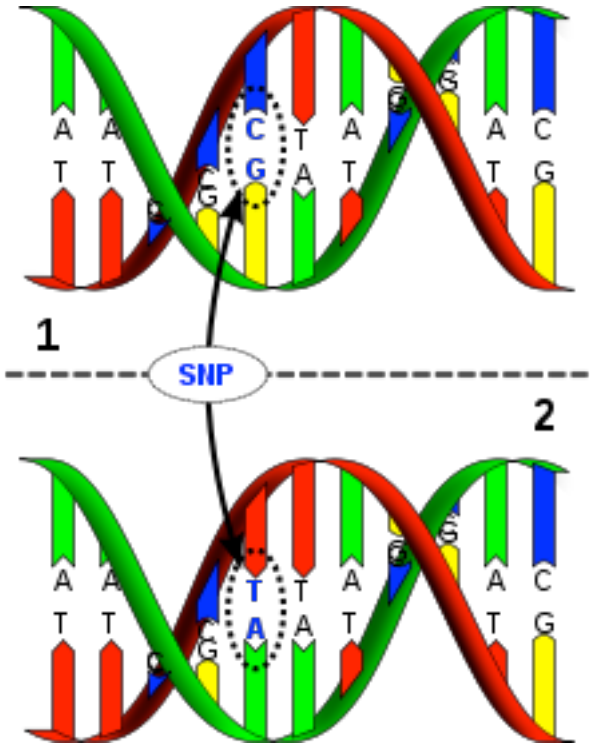
SNPs

SNPs (single nucleotide polymorphism) are the most common type of genetic variation between people

SNP is a one nucleotide difference in DNA sequence occurring in at least 1 % of the population

There is ~ 10 - 30 million SNPs in the human genome

SNPs occur every 100-300 bases along the 3-billion-base human genome



HapMap project

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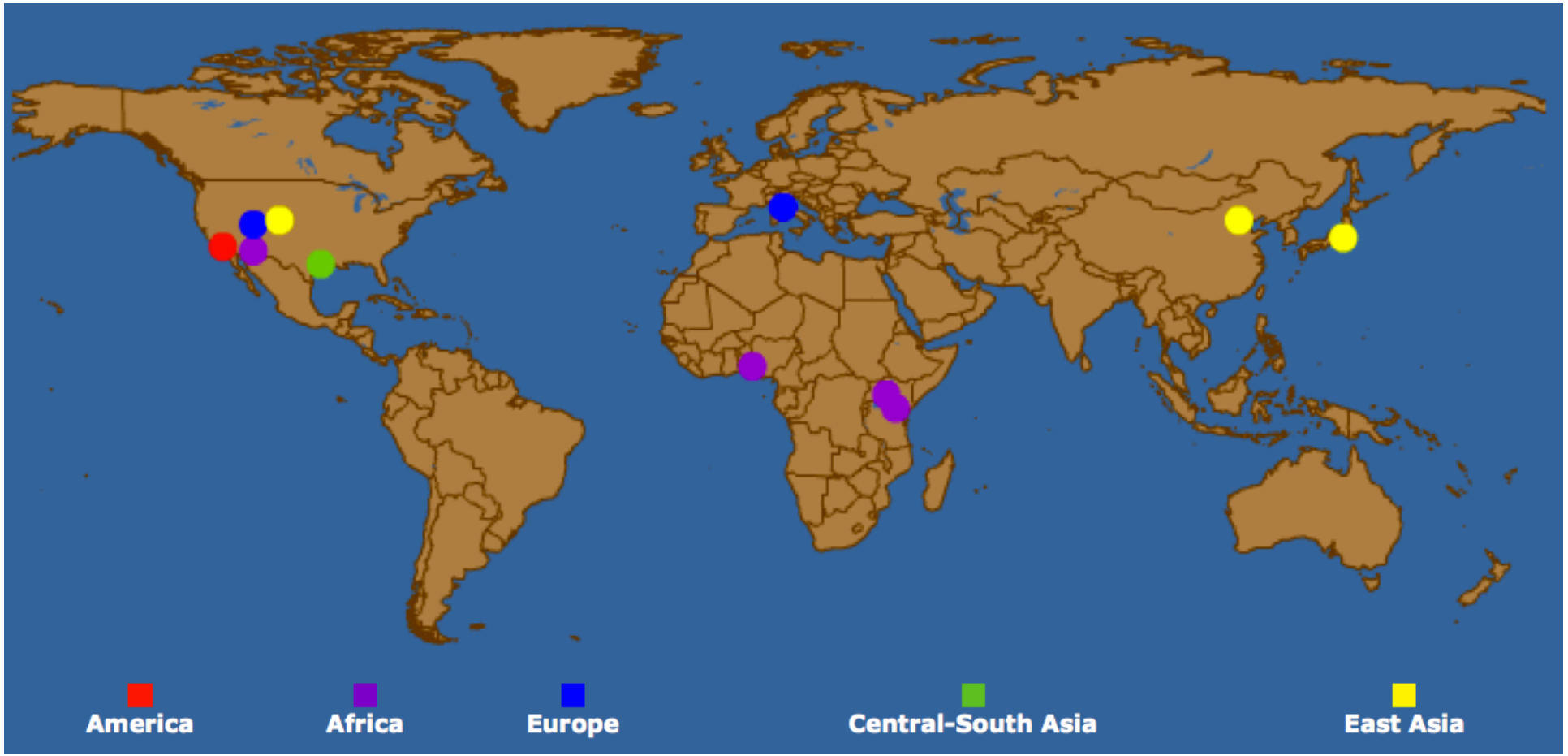
- haplotype map (HapMap) of the human genome
- - describes common patterns of human genetic variation



European genetic map

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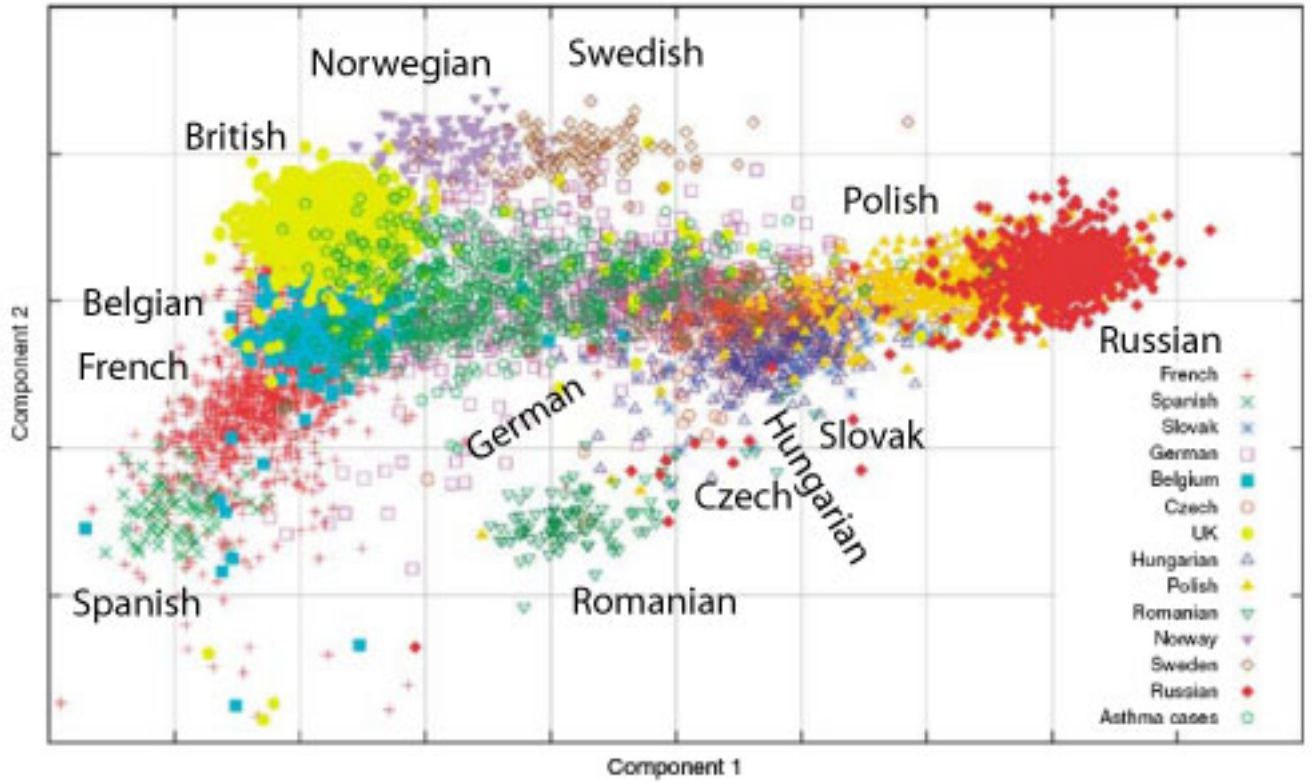
6,000 individuals from 13 populations
~ 300,000 SNPs
PCA



European Journal of Human Genetics (2008) 16, 1413–1429; doi:10.1038/ejhg.2008.210

SNP information

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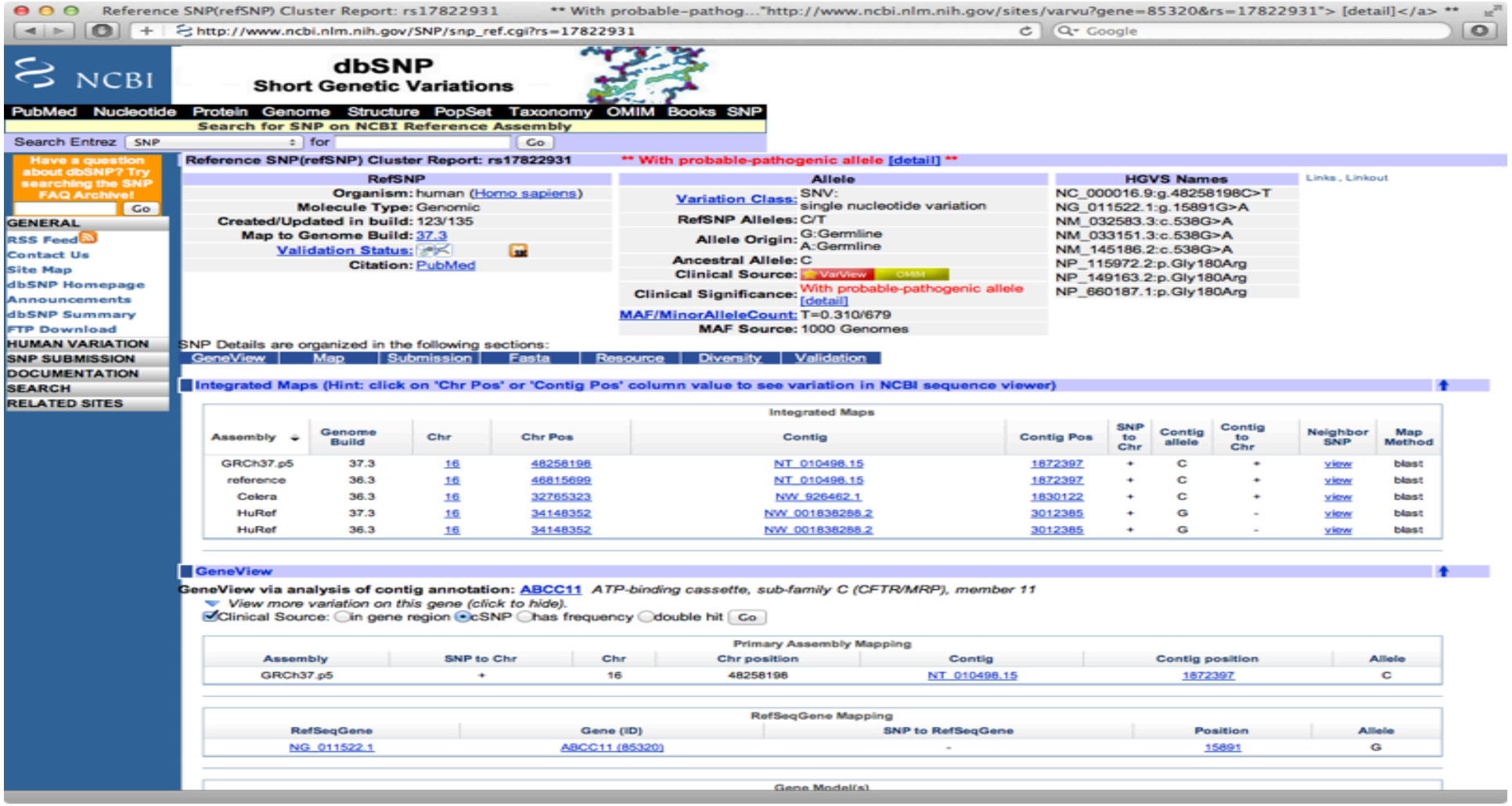
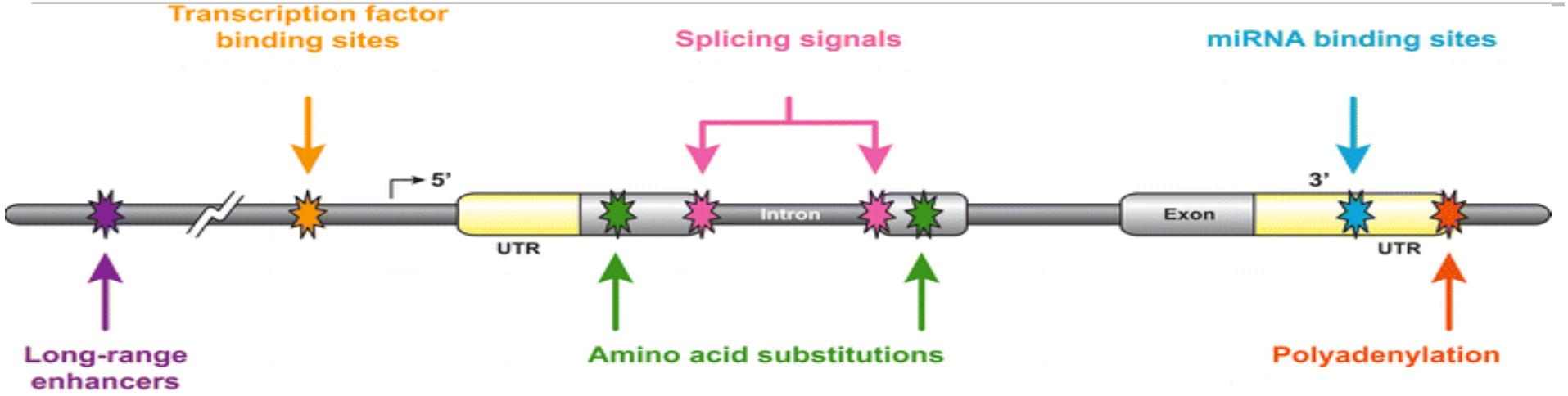
- rs number
- location (chr:position)



SNP consequence



Coding SNPs:

- non-synonymous coding (missense) – change of an amino acid
- synonymous coding (silent mutation) – no change in protein sequence
- stop codon (nonsense) - premature stop codon
- frame-shift coding – insertion/ deletion resulting in frame shift

Non-coding SNPs:

Mostly non-functional, but may affect:

- regulatory region
- splice site
- transcription factor binding
- messenger RNA degradation
- sequence of non-coding RNA

SNPs and mutations

Mutations are differences in DNA sequence in an individual that are rare, and may be unique to the individual (or their family line).

Polymorphisms are differences in DNA sequence that are found in many individuals, at a specified frequency (usually 1% or greater of a population)

Polymorphisms start as mutations, but if they become “fixed” in the population, and achieve sufficient frequency, they become polymorphisms.

SNP and genotype

Human are diploid (we have 2 homologous copies of each chromosome)

At each SNP there are 3 possible genotypes:
- homozygous reference
- heterozygous
- homozygous non-reference

Homozygous = 2 identical alleles at given locus, eg. AA
Heterozygous = 2 different alleles at given locus, eg. AC

Phenotype

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Phenotype = organism's observable characteristic or trait

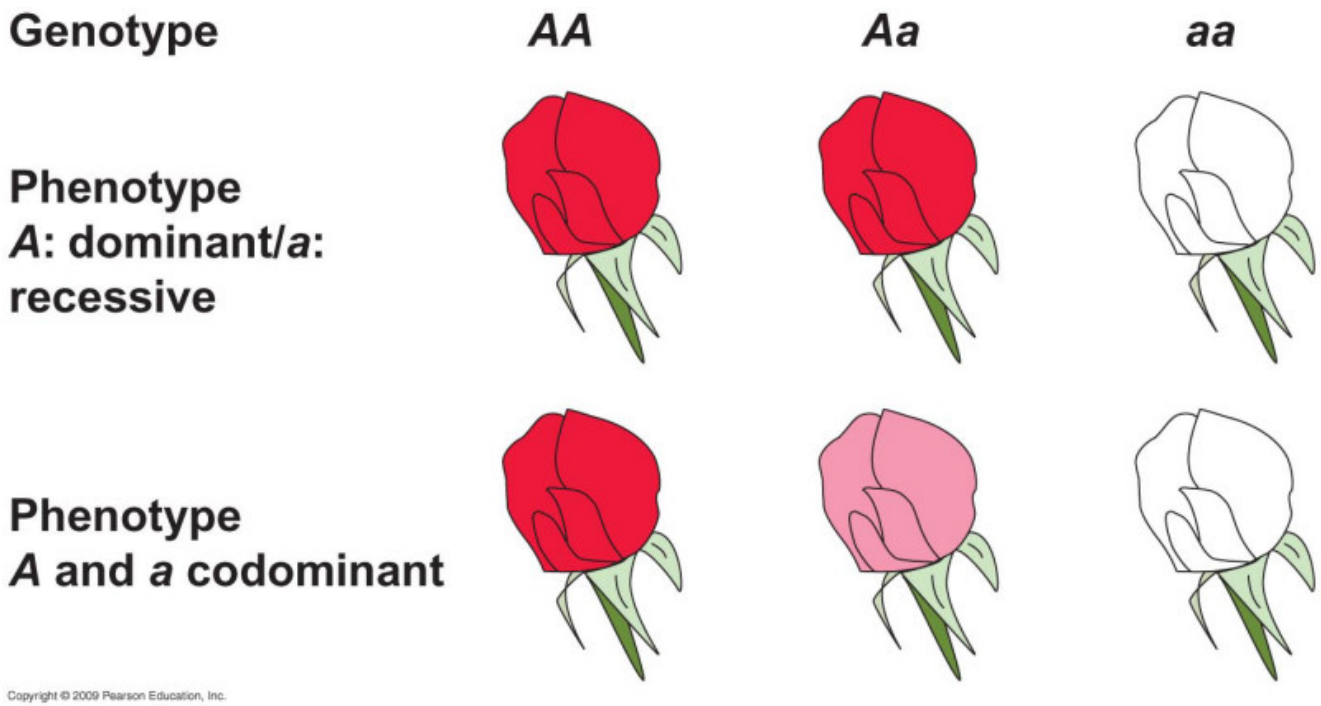
obesity

eye color

height

An organism's genotype is a major influencing factor in the development of its phenotype

Genotype => phenotype



SNPedia

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Genotype	Effect
rs17822931(C;C)	wet earwax
rs17822931(C;T)	wet earwax
rs17822931(T;T)	dry earwax

Direct-to-customer genetic testing

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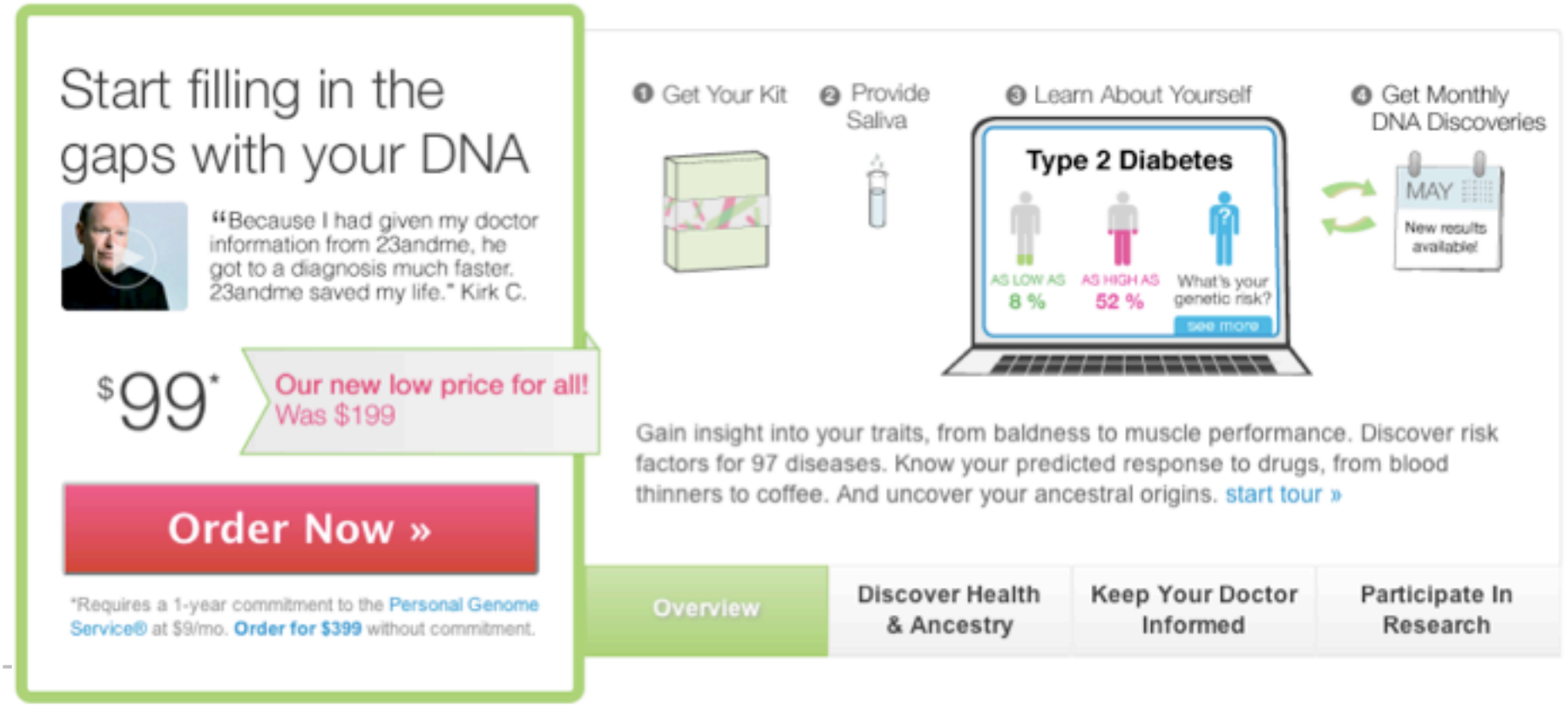
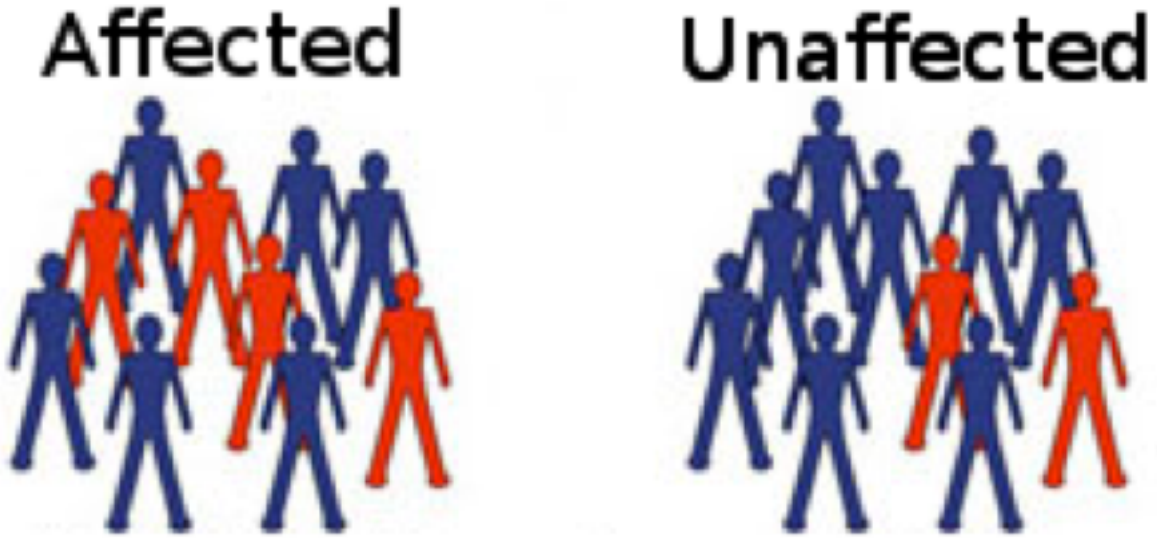
- 23andme
- deCODEme
- Navigenics

~ 1 million SNPs



Association studies



Test whether allele frequency of a SNP is significantly different between the two groups

GWAS results = p-values

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Manhattan plot displays all SNPs on x-axis (ordered by genomic location), and –log10 of their p-values on y-axis

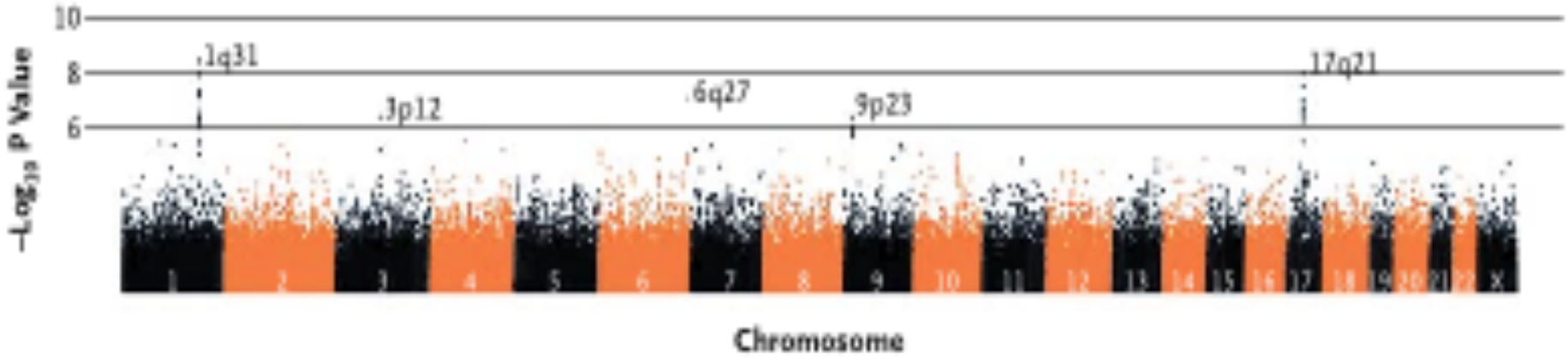
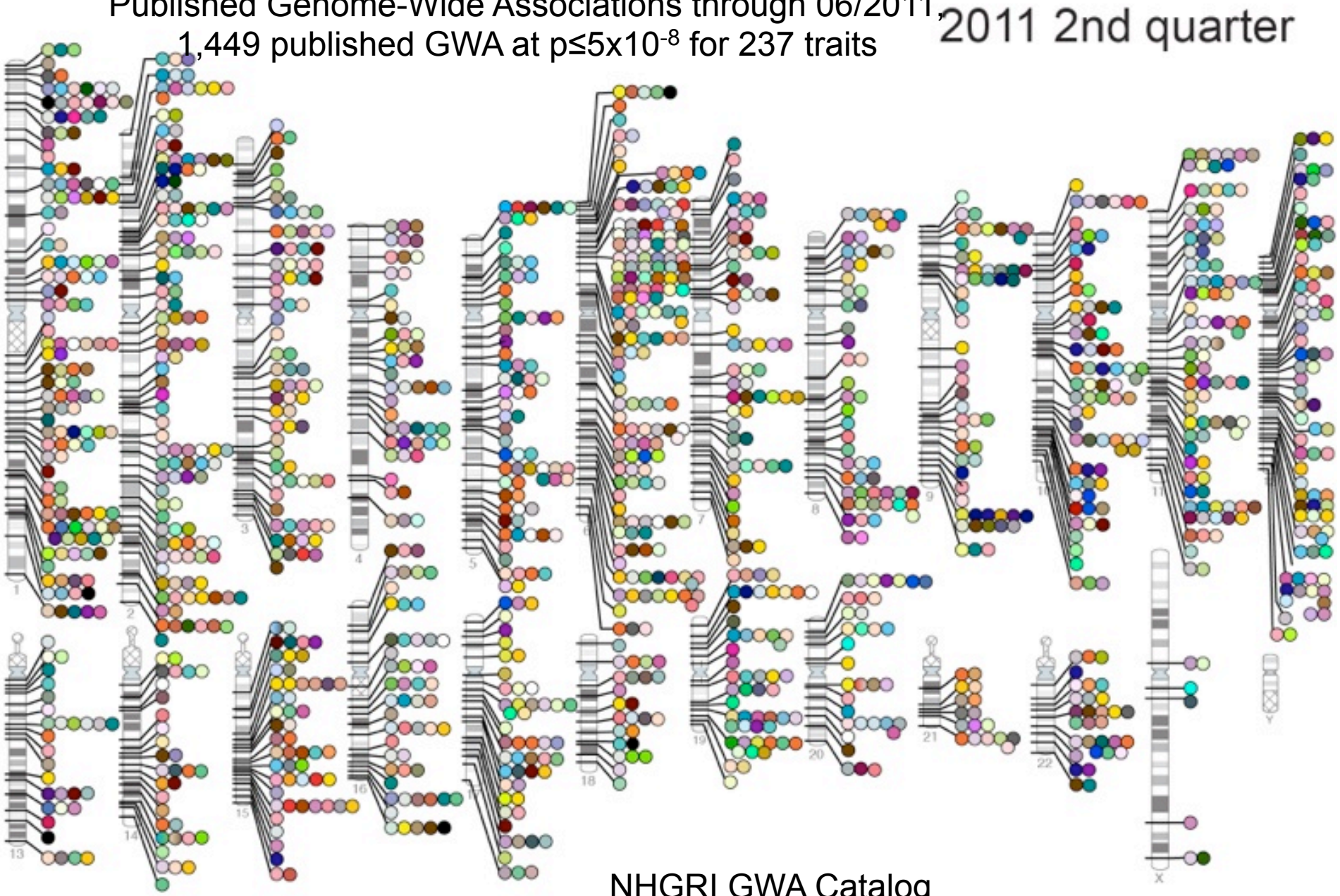


Figure 2. Manhattan Plot of the Results from the Combined Subjects of European Ancestry Who Had Asthma.

The $-\log_{10}$ P values are plotted against the physical distance. Only the two loci at chromosome 1q31 and 17q21 were significantly associated with asthma after Bonferroni correction. Individual chromosome labels are indicated in white within the Manhattan plot.

Published Genome-Wide Associations through 06/2011,
1,449 published GWA at $p \leq 5 \times 10^{-8}$ for 237 traits



NHGRI GWA Catalog
www.genome.gov/GWAStudies


Abdominal aortic aneurysm
Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alopecia areata
Alzheimer disease
Amyloid A levels
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asparagus anosmia
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Behcet's disease
Bipolar disorder
Biliary atresia
Bilirubin
Bitter taste response
Birth weight
Bladder cancer
Bleomycin sensitivity
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Calcium levels
Cardiac structure/function
Cardiovascular risk factors
Carnitine levels
Carotenoid/tocopherol levels
Celiac disease
Celiac disease and rheumatoid arthritis
Cerebral atrophy measures
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Cleft lip/palate
Coffee consumption
Cognitive function
Conduct disorder
Colorectal cancer
Corneal thickness
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Crohn's disease and celiac disease
Cutaneous nevi
Cystic fibrosis severity
Dermatitis
DHEA-s levels
Diabetic retinopathy
Dilated cardiomyopathy
Drug-induced liver injury
Drug-induced liver injury (amoxicillin-clavulanate)
Endometrial cancer
Endometriosis
Eosinophil count
Eosinophilic esophagitis
Erectile dysfunction and prostate cancer treatment
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
Eye color traits
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Follicular lymphoma
Fuch's corneal dystrophy
Freckles and burning
Gallstones
Gastric cancer
Glioma
Glycemic traits
Hair color
Hair morphology
Handedness in dyslexia
HDL cholesterol
Heart failure
Heart rate
Height
Hemostasis parameters
Hepatic steatosis
Hepatitis
Hepatocellular carcinoma
Hirschsprung's disease
HIV-1 control
Hodgkin's lymphoma
Homocysteine levels
Hypospadias
Idiopathic pulmonary fibrosis
IFN-related cytopeni
IgA levels
IgE levels
Inflammatory bowel disease
Insulin-like growth factors
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Keloid
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
Longevity
LP (a) levels
LpPLA(2) activity and mass
Lung cancer
Magnesium levels
Major mood disorders
Malaria
Male pattern baldness
Mammographic density
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Meningococcal disease
Metabolic syndrome
Migraine
Moyamoya disease
Multiple sclerosis
Myeloproliferative neoplasms
Myopia (pathological)
N-glycan levels
Narcolepsy
Nasopharyngeal cancer
Natriuretic peptide levels
Neuroblastoma
Nicotine dependence
Obesity
Open angle glaucoma
Open personality
Optic disc parameters
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pancreatic cancer
Pain
Paget's disease
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Personality dimensions
Phosphatidylcholine levels
Phosphorus levels
Photic sneeze
Phytosterol levels
Platelet count
Polycystic ovary syndrome
Primary biliary cirrhosis
Primary sclerosing cholangitis
PR interval
Progranulin levels
Progressive supranuclear palsy
Prostate cancer
Protein levels
PSA levels
Psoriasis
Psoriatic arthritis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Refractive error
Renal cell carcinoma
Renal function
Response to antidepressants
Response to antipsychotic therapy
Response to carbamazepine
Response to clopidogrel therapy
Response to hepatitis C treat
Response to interferon beta therapy
Response to metformin
Response to statin therapy
Restless legs syndrome
Retinal vascular caliber
Rheumatoid arthritis
Ribavirin-induced anemia
Schizophrenia
Serum metabolites
Skin pigmentation
Smoking behavior
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Sudden cardiac arrest
Suicide attempts
Systemic lupus erythematosus
Systemic sclerosis
T-tau levels
Tau AB1-42 levels
Telomere length
Testicular germ cell tumor
Thyroid cancer
Thyroid volume
Tooth development
Total cholesterol
Triglycerides
Tuberculosis
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Urinary albumin excretion
Urinary metabolites
Uterine fibroids
Venous thromboembolism
Ventricular conduction
Vertical cup-disc ratio
Vitamin B12 levels
Vitamin D insufficiency
Vitiligo
Warfarin dose
Weight
White cell count
White matter hyperintensity
YKL-40 levels

SNP calling with NGS

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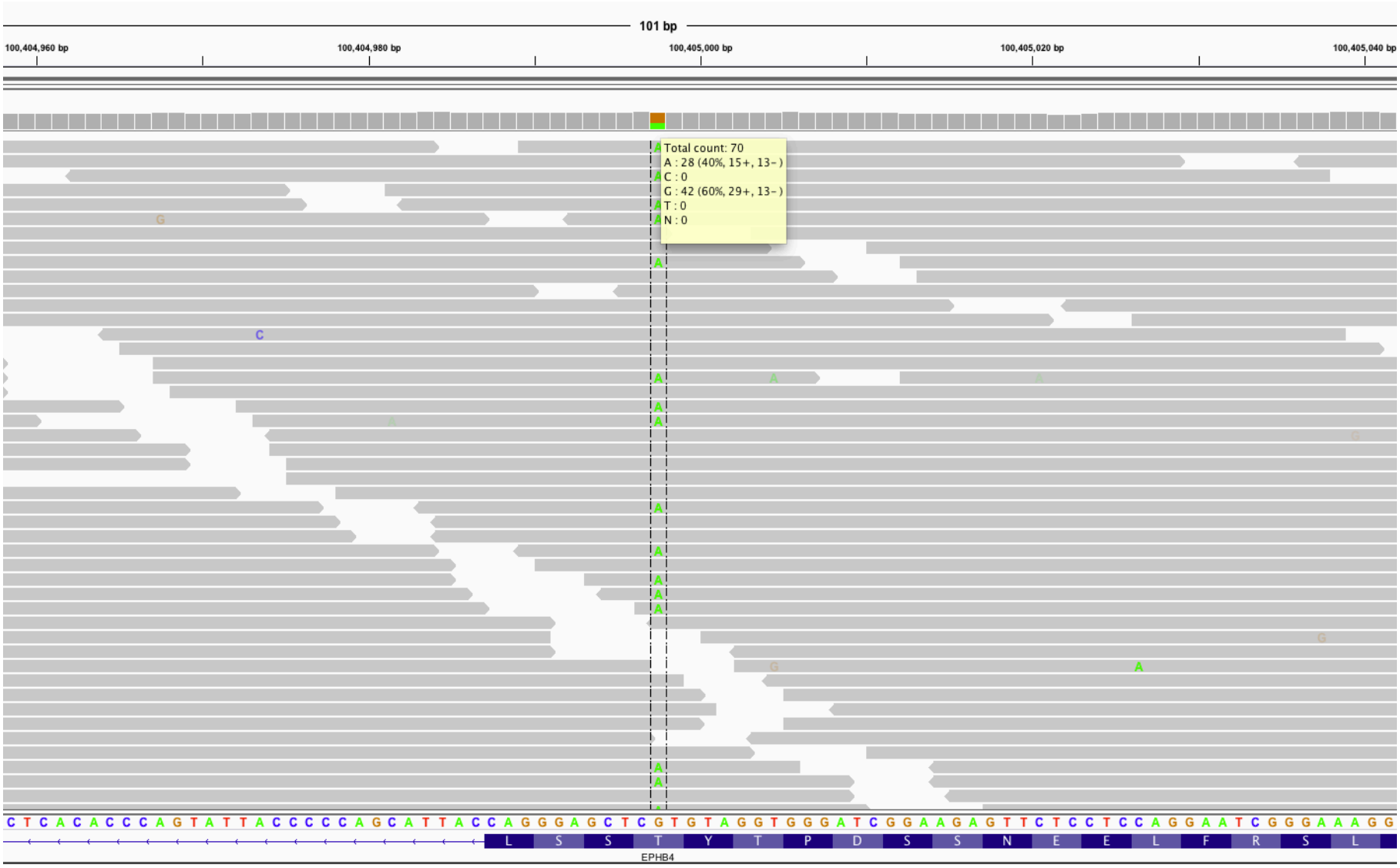

VCF file

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Terminal — ssh — ⌘2

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##INFO=<ID=FQ,Number=1,Type=Float,Description="Phred probability of all samples being the same">
##INFO=<ID=AF1,Number=1,Type=Float,Description="Max-likelihood estimate of the site allele frequency of the first ALT allele">
##INFO=<ID=G3,Number=3,Type=Float,Description="ML estimate of genotype frequencies">
##INFO=<ID=HWE,Number=1,Type=Float,Description="Chi^2 based HWE test P-value based on G3">
##INFO=<ID=CI95,Number=2,Type=Float,Description="Equal-tail Bayesian credible interval of the site allele frequency at the 95% level">
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##INFO=<ID=INDEL,Number=0,Type=Flag,Description="Indicates that the variant is an INDEL.">
##INFO=<ID=PC2,Number=2,Type=Integer,Description="Phred probability of the nonRef allele frequency in group1 samples being larger (,smaller) than in group2.">
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##FORMAT=<ID=SP,Number=1,Type=Integer,Description="Phred-scaled strand bias P-value">
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13      19254916        .       T       C       75      .       DP=54;AF1=1;CI95=1,1;DP4=0,0,41,2;MQ=20;FQ=-156 GT:PL:GQ        1/1:108,129,0:99
13      19393304        .       C       G       109     .       DP=40;AF1=0.5001;CI95=0.5,0.5;DP4=3,6,17,13;MQ=20;FQ=8.65;PV4=0.27,1e-22,1,0.2  GT:PL:GQ        0/1:139,0,35:38
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13      19419969        .       T       C       18.1    .       DP=66;AF1=0.5;CI95=0.5,0.5;DP4=0,36,0,28;MQ=20;FQ=19.9;PV4=1,8.3e-31,1,0.19     GT:PL:GQ        0/1:48,0,53:50
13      19429058        .       C       T       53      .       DP=57;AF1=1;CI95=1,1;DP4=0,0,0,53;MQ=20;FQ=-187 GT:PL:GQ        1/1:86,160,0:99
13      19444828        .       C       T       222     .       DP=211;AF1=1;CI95=1,1;DP4=0,0,78,115;MQ=20;FQ=-282      GT:PL:GQ        1/1:255,255,0:99
13      19467950        .       A       G       140     .       DP=41;AF1=1;CI95=1,1;DP4=0,0,29,10;MQ=20;FQ=-144        GT:PL:GQ        1/1:173,117,0:99
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13      19539455        .       C       T       113     .       DP=31;AF1=1;CI95=1,1;DP4=0,0,2,23;MQ=20;FQ=-102 GT:PL:GQ        1/1:146,75,0:99
13      19625269        .       A       G       74      .       DP=64;AF1=1;CI95=1,1;DP4=0,0,17,1;MQ=20;FQ=-81  GT:PL:GQ        1/1:107,54,0:99
13      19700922        .       T       A       53      .       DP=37;AF1=1;CI95=1,1;DP4=0,0,9,0;MQ=20;FQ=-54   GT:PL:GQ        1/1:86,27,0:51
13      19700978        .       A       G       83      .       DP=67;AF1=1;CI95=1,1;DP4=0,0,59,3;MQ=20;FQ=-214 GT:PL:GQ        1/1:116,187,0:99
```